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Outcome of ovarian cancer after breast cancer in *BRCA1* and *BRCA2* mutation carriers

Leendert H Zaaijer[1,2], Helena C van Doorn[1], Marian J E Mourits[3], Marc van Beurden[4], Joanne A de Hullu[5], Muriel A Adank[6], Luc R C W van Lonkhuijzen[7], Hans F A Vasen[8], Brigitte F M Slangen[9], Katja N Gaarenstroom[10], Ronald P Zweemer[11], Peggy M L H Vencken[12], Caroline Seynaeve[2] and Mieke Kriege*[,2]

[1]Department of Obstetrics and Gynaecology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [2]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [3]Department of Obstetrics and Gynaecology, Medical Centre Groningen, University of Groningen, Groningen, The Netherlands; [4]Department of Obstetrics and Gynaecology, Netherlands Cancer Institute NKI-AVL, Amsterdam, The Netherlands; [5]Department of Obstetrics and Gynaecology, Radboud University Medical Centre, Nijmegen, The Netherlands; [6]Department of Clinical Genetics, VU Medical Centre, Amsterdam, The Netherlands; [7]Center for Gynecologic Oncology, Academic Medical Centre, Amsterdam, The Netherlands; [8]Foundation for the Detection of Hereditary Tumours (STOET), Leiden, The Netherlands; [9]Department of Obstetrics and Gynaecology, Maastricht University Medical Centre, Maastricht, The Netherlands; [10]Department of Obstetrics and Gynaecology, Leiden University Medical Centre, Leiden, The Netherlands; [11]Department Gynaecological Oncology, UMC Utrecht Cancer Centre, Utrecht, The Netherlands and [12]Department of Obstetrics and Gynaecology, Bravis Hospital, Bergen op Zoom, The Netherlands

Background: It is unknown whether a history of breast cancer (BC) affects the outcome of *BRCA1/2*-associated epithelial ovarian cancer (EOC). This was investigated in the current analysis.

Methods: We included 386 *BRCA1/2*-associated EOC patients diagnosed between 1980 and 2015. Progression-free survival (PFS), progression-free interval (PFI), overall survival (OS) and ovarian cancer-specific survival (OCSS) were compared between EOC patients with and without previous BC.

Results: *BRCA*-associated EOC patients with, *vs* without, a BC history had a significantly worse PFS and PFI (multivariate hazard ratio (HR_{mult}) 1.47; 95% confidence interval (CI) 1.03–2.08 and HR_{mult} 1.43; 95% CI 1.01–2.03), and a non-significantly worse OS (HR_{mult} 1.15; 95% CI 0.84–1.57) and OCSS (HR_{mult} 1.18; 95% CI 0.85–1.62). Ovarian cancer-specific survival was significantly worse for the subgroup treated with adjuvant chemotherapy for BC (HR_{mult} 1.99; 95% CI 1.21–3.31).

Conclusions: Our results suggest that *BRCA1/2*-associated EOC patients with a previous BC have a worse outcome than EOC patients without BC, especially when treated with adjuvant chemotherapy.

It is assumed that 8–16% of all epithelial ovarian cancer (EOC) cases are due to *BRCA1/2* germ line mutations (Risch *et al*, 2001; Thompson *et al*, 2002; Alsop *et al*, 2012). An improved survival after primary therapy has been reported for *BRCA1/2*-associated compared with sporadic EOC patients (Vencken *et al*, 2011; Yang *et al*, 2011; Hyman *et al*, 2012). This is thought to be explained by the crucial role of *BRCA* genes in homologous recombination, a mechanism to repair double-strand DNA breaks, which is deficient in patients without functional BRCA proteins. Platinum chemotherapy, like cisplatin or carboplatin, being a

*Correspondence: Dr M Kriege; E-mail: a.kriege@erasmusmc.nl

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cornerstone in EOC treatment, typically induces double-strand DNA breaks leading to more cancer cell death in *BRCA1/2* mutation carriers.

Around 30–50% of the *BRCA1/2*-associated EOC patients have been treated for previous breast cancer (BC; Alsop *et al*, 2012; Vencken *et al*, 2013), whereas data on the incidence of EOC after

Table 1. Patient, tumour and treatment characteristics of OC in *BRCA1/2* patients with and without a history of BC

	Patients with a history of BC *N*	%	Patients without a history of BC *N*	%	*P*-value
Total number of patients	116	30	270	70	
Age at diagnosis					0.09
Median in years (range)	53.1 (39.0–77.1)		52.0 (23.2–89.7)		
Mean in years (s.d.)	54.3 (8.3)		52.6 (9.1)		
Follow-up time					0.15
Median in years (range)	4.9 (0.4–33.4)		5.6 (0.1–33.1)		
Type of mutation					0.18
BRCA1	89	77	188	70	
BRCA2	27	23	82	30	
BRCA1/2 testing after EOC diagnosis[a]	71	64	211	82	<0.001
Mean time after EOC in years	3.6		4.3		0.28
Median time after EOC in years	1.4		2.2		
Year of diagnosis					0.16
1980–1989	9	8	32	12	
1990–1999	35	30	83	31	
2000–2009	60	52	142	53	
⩾2010	12	10	13	5	
CA-125 (kU l^{-1}) at primary diagnosis					0.02
<35	19	16	20	7	
35–500	28	24	81	30	
>500	31	27	94	35	
Unknown	38	33	75	28	
Histology					0.77
Serous	75	65	166	62	
Mucinous	5	4	8	3	
Endometrioid	8	7	28	10	
Clear cell	0	0	3	1	
Undifferentiated	7	6	18	7	
Adenocarcinoma NOS	16	14	34	13	
Other	1	1	6	2	
Unknown	4	3	7	3	
Tumour grade (Silverberg)					0.99
1 (well differentiated)	5	4	11	4	
2 (moderately differentiated)	24	21	55	20	
3 (poorly differentiated)	72	62	172	64	
Unknown	15	13	32	12	
FIGO stage					0.56
I	17	15	29	11	
II	15	13	35	13	
III	57	49	153	57	
IV	23	20	48	18	
Unknown	4	3	5	2	
Surgery					0.71
Primary surgery	81	70	172	64	
Interval debulking	9	8	24	9	
Both	24	21	70	26	
None	0	0	1	0	
Unknown	2	2	3	1	
Radiotherapy					0.79
Yes	5	4	10	4	
No	103	89	236	87	
Unknown	8	7	24	9	
Chemotherapy					0.68
Platinum with Paclitaxel	77	66	182	67	
Platinum without Paclitaxel	30	26	72	27	
Other	3	3	2	1	
No	6	5	11	4	
Unknown	0	0	3	1	
Duration of chemotherapy for primary OC					0.07
Median in weeks (range)	18.7 (1.3–47.7)		20.0 (2.1–98.6)		
Mean in weeks (s.d.)	20.5 (7.9)		22.7 (11.8)		

Abbreviations: BC = breast cancer; FIGO = international federation of gynecology and obstetrics; OC = ovarian cancer; NOS = not otherwise specified.
[a]Date of DNA test was missing for 18 patients (5 with and 13 without a BC history).

BC in *BRCA1/2* mutation carriers are scarce. Metcalfe reported a 10-year actuarial risk of developing EOC after BC of 12.7% for *BRCA1* and of 6.8% for *BRCA2* mutation carriers ($P = 0.03$) (Metcalfe *et al*, 2005). Currently it is unknown whether a BC history affects the outcome of subsequent EOC in *BRCA1/2* mutation carriers, especially as treatment for early *BRCA*-associated BC frequently includes adjuvant chemotherapy.

In the current study we evaluated the outcome of EOC in *BRCA1/2* mutation carriers with and without a BC history. In addition, we investigated the impact of adjuvant chemotherapy for BC on the outcome of *BRCA1/2*-associated EOC.

MATERIALS AND METHODS

Patients. Initially, we selected EOC patients identified with a *BRCA1* or *BRCA2* mutation, diagnosed between 1980 and 2008 from databases at all eight Dutch University Medical Centres, one Cancer Centre and the Netherlands Foundation for the Detection of Hereditary Tumours (STOET), as has been described previously (Vencken *et al*, 2013). In four centres both *BRCA1* and *BRCA2* patients were included, whereas in six centres, due to a lower prevalence, only *BRCA2* patients were included. In addition, from the Erasmus MC in Rotterdam *BRCA1/2*-associated EOC patients treated between 2008 and 2015 were included. Exclusion criteria were a previous malignancy (except for BC and basal cell carcinoma), a borderline ovarian tumour and a primary or recurrent BC synchronous with EOC.

For the selected patients, data concerning tumour characteristics, treatment for BC and EOC, and follow-up were collected from medical records. The medical ethical committee of the Erasmus MC, Rotterdam (MEC-2014–429) approved the study.

Definitions. The main outcome measures were progression-free survival (PFS), progression-free interval (PFI), overall survival (OS) and ovarian cancer-specific survival (OCSS).

Progression-free survival was defined as the time between the date of EOC diagnosis and the date of progressive or recurrent disease. Progression-free interval was defined as the time between the last day of first-line treatment for EOC and the date of progressive/recurrent disease. The end date of chemotherapy was estimated if the last day of chemotherapy was unknown. Overall survival was defined as the time between date of EOC diagnosis and date of death. Ovarian cancer-specific survival was defined as the time between the date of EOC diagnosis and the date of death due to EOC.

Statistics. Differences in tumour and treatment characteristics between EOC patients with and without a history of BC were tested with the Pearson's χ^2-test or, in case of small numbers, with the Fisher's exact test (categorical variables) or with the Student's *t*-test (continuous variables). Progression-free survival, PFI, OS and OCSS were calculated using the Kaplan–Meier survival method for patients with and without a previous BC separately. Subsequent analyses were performed for the group of patients treated with and without adjuvant chemotherapy for a previous BC separately. To account for the time elapsed between EOC diagnosis and genetic testing, we performed left-truncated survival analyses. Patients were censored at date of loss to follow-up, or end date of the study (April 2015). For PFS, PFI and OCSS patients were also censored at date of death not due to EOC. Differences between the groups were tested by means of a log rank test. Univariate as well as multivariate Cox proportional hazard regression models were performed, to calculate hazard ratio's (HRs) and 95% confidence intervals (95% CIs). Following confounding factors were included in the multivariate regression model: age at EOC diagnosis (continuous), year of EOC diagnosis (<2000; $\geqslant 2000$), CA-125 level at diagnosis (<35; 35–500; >500; unknown), differentiation grade (grade I and grade II; grade III; unknown), FIGO stage (I- IIa; $>$ IIa; unknown), type of mutation (*BRCA1*; *BRCA2*) and chemotherapy regimen for EOC (platinum/paclitaxel; platinum without paclitaxel; non-platinum-based; unknown). Analyses were performed using SPSS (version 21.0; SPSS, Inc., Chicago, IL, USA) or Stata (version 14; Stat Corporation, College Station, TX, USA). A two-sided *P*-value < 0.05 was considered statistically significant.

RESULTS

Patient, tumour and treatment characteristics of 116 EOC patients with previous BC and 270 without previous BC are presented in Table 1. In Supplementary Table 1, data on BC treatment are summarised. The median age at EOC diagnosis was 51.8 for *BRCA1* and 56.3 years for *BRCA2* patients, and 73% of the patients were diagnosed with advanced stage disease ($\geqslant$ FIGO stage IIb). CA-125 values at EOC diagnosis were lower in the group with previous BC ($P = 0.02$). The patients with previous BC were less often tested for *BRCA1/2* mutations after their EOC diagnosis ($P < 0.001$). There were no other significant differences between the characteristics of the two patient groups, with and without previous BC, observed (Table 1).

Progression-free survival was not significantly different for patients with previous BC compared with patients without a previous BC (5-year PFS 22% *vs* 28%; Figure 1a and Supplementary Table 2). In the multivariate analysis, however, PFS was significantly lower in the group with previous BC (HR multivariate (HR_{mult}) 1.47; 95% CI 1.03–2.08). Similar data were observed for PFI, at univariate analysis no significant difference was found between the two patient groups, whereas in the multivariate analysis the group with a history of BC had a shorter PFI (HR_{mult} 1.43; 95% CI 1.01–2.03; Figure 1b and Supplementary Table 2). No significant difference was found regarding OS (HR_{mult} 1.15; 95% CI 0.84–1.57) and OCSS (HR_{mult} 1.18; 95% CI 0.85–1.62) between patients with and without a history of BC (Supplementary Table 2 and Figure 1c and d). The time between BC diagnosis and EOC diagnosis was not associated with PFS (HR_{mult} 1.00; 95% CI 0.96–1.04), nor with OCSS (HR_{mult} 0.99; 95% CI 0.95–1.04; data not shown).

To address the possible impact of adjuvant chemotherapy administered for BC on the PFS and OCSS of subsequent EOC patients with BC before OC treated with chemotherapy and patients not treated with adjuvant chemotherapy for BC were separately analysed and compared with EOC patients without previous BC (Figure 2 and Supplementary Table 3). We observed that PFS and OCSS were especially worse for patients treated with adjuvant chemotherapy for previous BC *vs* patients without previous BC (median 1.5 *vs* 2.0, and median 5.0 *vs* 5.3 years, respectively). In the multivariate analyses these differences were significant (HR_{mult} 2.38; 95% CI 1.40–4.02 and HR_{mult} 1.99; 95% CI 1.21–3.31, respectively). The patients with a BC history not treated with adjuvant chemotherapy had similar PFS and OCSS compared with EOC patients without a BC history (HR_{mult} 1.16; 95% CI 0.76–1.79 and HR_{mult} 0.87; 95% CI 0.59–1.29, respectively; Figure 2 and Supplementary Table 3).

DISCUSSION

In the current study, we observed a significantly worse PFS and PFI, in *BRCA*-associated EOC patients with a BC history *vs* EOC patients without a previous BC, not yet resulting in a significantly worse survival. A significantly worse OCSS, however, was found in *BRCA*-associated EOC patients treated with adjuvant chemotherapy for BC compared with EOC patients without previous BC.

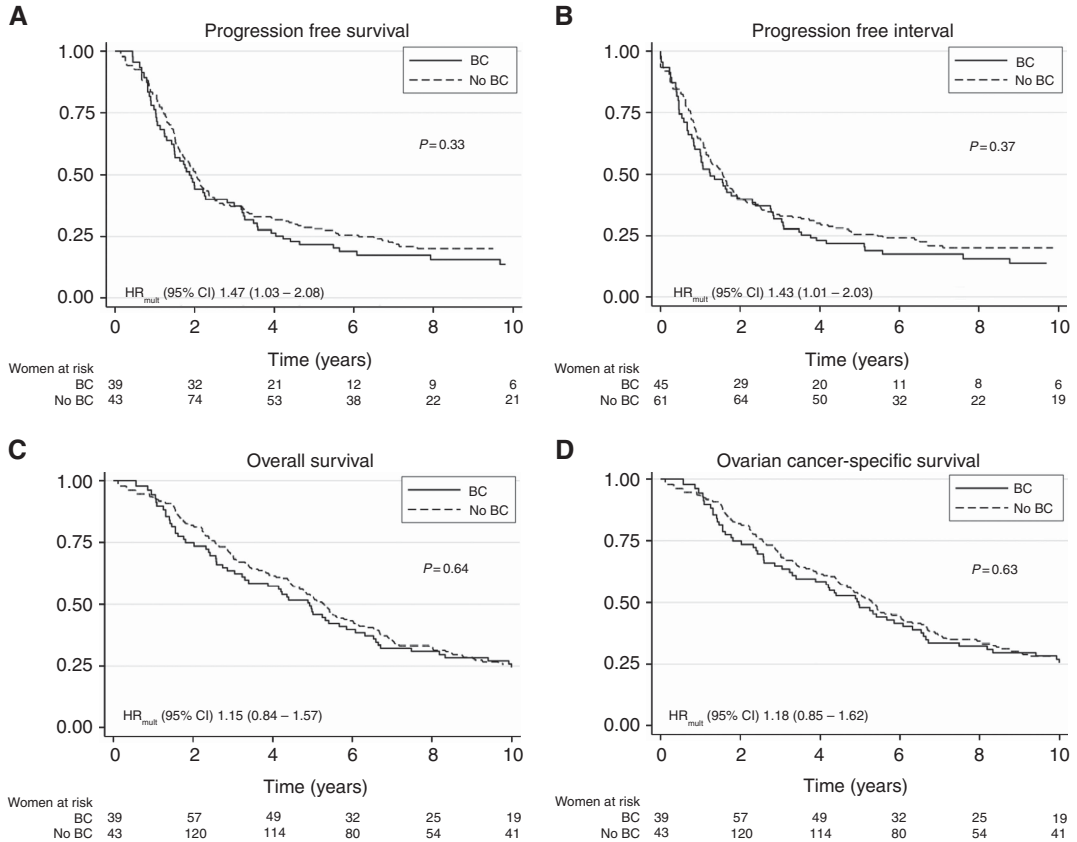

Figure 1. Progression free survival (**A**), progression free interval (**B**), overall survival (**C**) and ovarian cancer-specific survival (**D**) for *BRCA1/2* epithelial ovarian cancer patients with and without a BC history. BC, breast cancer; CI, confidence interval; HR, hazard ratio.

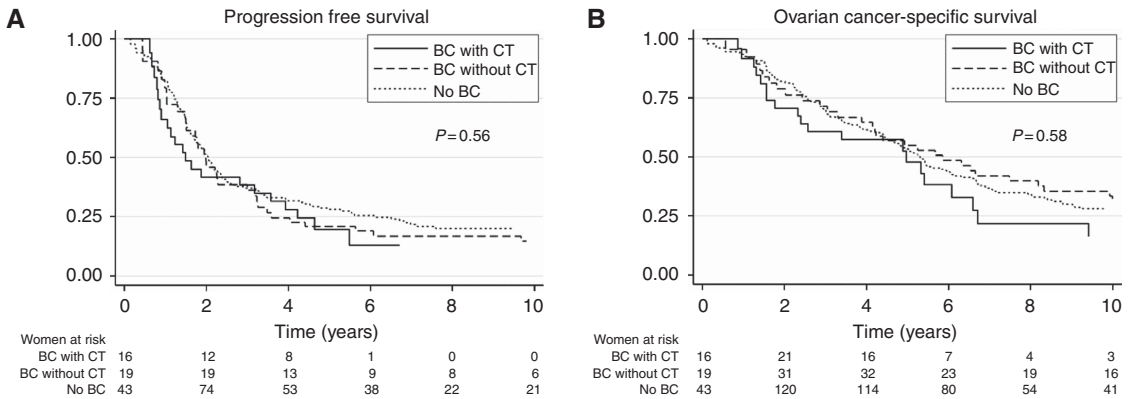

Figure 2. Progression free survival (**A**) and ovarian cancer-specific survival (**B**) for *BRCA1/2* epithelial ovarian cancer patients with and without adjuvant chemotherapy for BC and without a BC history. BC, breast cancer; CT, chemotherapy.

No differences in grade, stage and histology were observed between both groups. A first hypothetical explanation for this survival difference might be that chemotherapy induces mutations and alters the behaviour of already present malignant EOC cells, or induces chromosomal instability in stem cells with subsequent development of EOC. Another possible explanation might be that treatment for the initial BC aggravates the (bone marrow) condition of the patient and, therefore, optimal therapy for EOC cannot be given to these patients. However, the time between BC diagnosis and OC diagnosis was not associated with outcome, suggesting that the condition of the patients is not the main reason for the worse survival in patients with a BC history.

The retrospective nature of the study brings corresponding limitations, such as different treatments regimens, and some missing data. Another limitation includes that the majority of the patients were tested for a *BRCA1/2* mutation after EOC diagnosis (64% and 82% in the groups with and without a BC history, respectively), this will select for survivors. To account for this possible survivorship bias we have conducted left-truncation survival analyses. Because of the retrospective design, no firm conclusions can be drawn and our results should be confirmed in other (prospective) studies with greater sample size.

The results of this study underline the importance of offering genetic testing to BC patients being at risk of *BRCA1/2* mutation carriership. Newly diagnosed mutation carriers can then be informed about risk reducing salpingo-oophorectomy, which has been associated with improved survival (Finch *et al*, 2014). Further,

we suggest that studies on survival in *BRCA1/2*-associated EOC should stratify for BC history.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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